## REMARKS

Introductory Comments:

Claims 1-8, 11-17 and 20-27 were examined in the Office Action dated 10 April 2002. Applicant notes with appreciation that the following rejections have been withdrawn: **(a)** the rejection of claim 24 under 35 U.S.C. §102(b) as unpatentable over Hofmann et al. (1996) *Proc. Natl. Acad. Sci.* 93:5185-5190 ("Hofmann"); **(b)** the rejection of claim 3 under 35 U.S.C. §112, first paragraph, as nonenabled; **(c)** the rejection of claims 2-8, 11-14 and 27 under 35 U.S.C. §112, second paragraph, as indefinite; **(d)** the rejection of claims 1 and 5 under 35 U.S.C. §102(b) as unpatentable over Laube et al. (1994) *Human Gene Therapy* 5:853-862 ("Laube"); **(e)** the rejection of claims 1-4, 7-8, 11-17, 20-23 and 25-27 under 35 U.S.C. §102(b) as unpatentable over Fynan et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:11478-11482 ("Fynan"); **(f)** the rejection of claims 1-3, 7, 12-14 and 25-27 under 35 U.S.C. §102(e) as unpatentable over U.S. Patent No. 5,891,718 to Hobart et al. ("Hobart"); and **(g)** the rejection of claims 1-4, 7-8, 11, 15-17 and 20-23 under 35 U.S.C. §103(a) as unpatentable over Hobart in view of U.S. Patent No. 6,194,389 to Johnston et al. ("Johnston").

However, the following claim rejections were maintained: **(1)** claims 1, 7, 12-14 and 25-27 remain rejected under 35 U.S.C. §102(b) as unpatentable over Hofmann; **(2)** claims 24-27 remain rejected under 35 U.S.C. §102(e) as unpatentable over U.S. Patent No. 6,200,751 to Gu et al. ("Gu"); **(3)** claims 1-4, 7-8, 11-12, 15-17, 20, 23 and 25-27 remain rejected under 35 U.S.C. §102(e) as unpatentable over Johnston in view of Miwa et al. (1987) *Mol. Cell. Biol.* 7:2803-2813 ("Miwa"); and **(4)** claims 1, 12 and 24-27 remain rejected under 35 U.S.C. §102(b) as unpatentable over Burns et al. (1993) *Blood* 81:1558-1566 ("Burns") or Deb et al. (1992) *J. Virology* 66:6164-6170 ("Deb").

In addition, the following new claim rejections have been entered: **(5)** claim 5 now stands rejected under 35 U.S.C. §102(b) as unpatentable over Hofmann (claim 5

has been added to claim rejection (1) above); (6) claims 5 and 6 now stand rejected under 35 U.S.C. §102(b) as unpatentable over Johnston in view of Miwa (claims 5 and 6 have been added to claim rejection (3), above); and (7) claims 15 and 21-22 now stand rejected under 35 U.S.C. §103(a) as unpatentable over Johnston with evidence of Miwa and in view of Hofmann.

All standing rejections are respectfully traversed for the reasons discussed herein below.

Overview of the Amendments:

Applicant, by way of this Amendment, has cancelled two claims and made minor amendments to two other claims. In particular, applicant has cancelled claims 26 and 27 without prejudice and disclaimer. It is to be understood that cancellation of these claims is not an acquiescence to ground of rejection or issue of patentability, and applicant reserves the right to bring the claims again in a subsequent, related application.

In addition, applicant has amended claims 1 and 25. Claim 1 has been amended to recite that expression of the antigen of interest in the mammalian subject is sufficient to elicit an immune response against said antigen. Support for this amendment may be found throughout the specification and claims as originally filed, and particularly in the specification at page 18, line 18 through page 21, line 10, and in Examples 1 and 2 (pages 21-26) and Figures 1-4. Claim 25 has been amended to recite vaccine compositions comprising a nucleic acid construct containing an antigen sequence operably linked to a minimal promoter according to the present invention. Support for this amendment can be found throughout the specification and claims as originally filed, and particularly in the specification at page 18, line 18 through page 21, line 10; and in Examples 1 and 2 (pages 21-26). Accordingly, no new matter is added by the present amendments to the claims, and the entry thereof is respectfully requested.

Pursuant to the Revised Notice from the USPTO, dated 13 February 2003, and entitled "Amendments May Now Be Submitted In Revised Format," the present Amendment has not been provided in both "clean version" and in "marked-up version" in conformance with 37 C.F.R. §1.121(b)(1) parts (ii) and (iii). Instead, this Amendment includes a complete listing of all claims in the present application with an indication of the current status of each. The listing begins on a separate sheet and is captioned "CURRENT STATUS OF ALL CLAIMS IN THE APPLICATION".

The Rejections under 35 U.S.C. §102:

Claims 1, 5, 7, 12-14 and 25-27 stand rejected under 35 U.S.C. 102(b) as anticipated by Hofmann. This is a new ground of rejection for claim 5 only. In particular, the Office asserts that Hofmann describes "a recombinant retroviral vector construct (SIN-RetroTet vector) containing an autoregulatory cassette comprising a heptamerized tet operator sequence fused to the human CMV immediate early minimal promoter $P_{hCMV*-1}$ (reciting Figure 1)." The Office asserts "the human CMV immediate early minimal promoter $P_{hCMV*-1}$ falls within the scope of a functional variant [and] the disclosure of Hoffman fulfills the required elements of the claims" Office Action at page 11. The Office then concludes that the claims are anticipated by the reference. Applicant respectfully traverses.

Anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference. *Constant v. Advanced Micro-Devices, Inc.*, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988). Exclusion of a single claimed element from a prior art reference is enough to negate anticipation by that reference. *Atlas Powder Co. v E.I. du Pont De Nemours & Co.* 224 USPQ 409, 411(Fed. Cir. 1984). Further, anticipation basically requires identity with the prior art document *(Tyler Refrigeration v. Kysor Indus. Corp.*, 227 USPQ 845 (Fed. Cir. 1985)), where the identical invention must be shown in as complete detail as is contained in the rejected claim (*Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989)). Finally, in order to anticipate, a prior art

reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. *Akzo N.V. v. United States ITC*, 1 USPQ2d 1241 (Fed. Cir. 1986).

Claim 1 as presently amended recites that the antigen of interest is expressed in a mammalian subject in an amount sufficient that an immune response is elicited against the antigen. Claims 5, 7 and 12-14 all depend either directly or indirectly from claim 1 and thus contain this same base limitation. Claim 25 as presently amended recites a vaccine composition containing an antigen sequence operably linked to a minimal promoter. Claims 26 and 27 are cancelled.

Hofmann clearly fails to disclose vaccine compositions, and in similar manner fails to disclose administration of nucleic acid compositions to mammals whereby antigen sequences are expressed in an amount sufficient to elicit an immune response. Hofmann thus cannot possibly anticipate claims 1, 5, 7, 12-14 and 25. Reconsideration and withdrawal of the rejection of these claims under 35 U.S.C. §102(b) over the Hofmann reference is thus respectfully requested.

Claims 24-27 remain rejected under 35 U.S.C. §102(e) as anticipated by Gu. In particular, the Office asserts that "Gu disclosed the isolation and use of the minimal promoter of the endothelial cell protein C binding protein, EPCR, operably linked to a gene coding for a protein of interest," and then concludes that GU's promoter meets the limitation of applicant's recited "minimal promoter." Office Action at page 2. The Office goes on to assert that a "promoter including a region .... between -1 and -220 based on the positions relative to the ATG ... meets the limitation of the 'minimal promoter' of the instant invention." Office Action at page 3. Finally, the Office argues that "Gu clearly refers to the promoter sequence (-220 to -1) as a minimal promoter" citing Gu, column 2, lines 15-17. Office Action at page 4. Applicant respectfully traverses for the following reasons.

Initially, applicant notes that the Office refers to "the promoter sequence -220 to -1 as if it were an actual, discrete entity. This is incorrect. Gu discloses two promoters: (1) a sequence spanning from -350 to -1 of the mouse EPCR promoter,

and (2) a sequence spanning from -1080 to -1 of the mouse EPCR promoter. See Gu, Example 3 and the Sequence Listing. Neither of these promoters (sequences of 350 and 1080 nucleotides, respectively) appears to be a minimal promoter since these promoters would be expected to have retained normal enhancer sites. The particular text that the Office has now relied upon (column 2, lines 15-17) to support its rejection is merely a discussion of various sections from the enhanced promoter sequence, where Gu has referred to the first 220 bases as the "minimal promoter" and has then discussed numerous additional sequences that are referred to environmental stimuli response elements found in the 350 and 1080 base promoters. See the rest of the sentence from Gu, at column 2, lines 18-29. It is absolutely clear that a promoter sequence of just -220 to -1 was never produced, nor was it suggested for production. The Office seems to have seized on inconsistent use of the term "minimal promoter," where applicant is disclosing and claiming actual promoter sequences artificially devoid of native enhancer sequences, and Gu is referring to a section within one of two natively enhanced promoter sequences.

Turning to the language of the rejected claims, claim 24 requires that an isolated, purified minimal promoter sequence is provided. Gu obviously fails to teach or suggest such a composition. Accordingly the rejection of claim 24 is improper and must be withdrawn. With regard to claim 25 (claims 26 and 27 have been cancelled herein), the composition needs to be a vaccine composition comprising an antigen sequence linked to a minimal promoter. Gu fails to teach a minimal promoter sequence and fails to teach a vaccine composition. In this regard, a discussion of certain regions within an enhanced promoter sequence fail to enable the construction of a minimal promoter as required by applicant's claim. Gu also is totally silent with respect to vaccine compositions and vaccine methodology, and thus fails to enable production of a suitable vaccine composition as also required by applicant's claim. As discussed above, anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference. In addition, a prior art reference must be enabling in

order to anticipate, thus placing the allegedly disclosed matter in the possession of the public. Gu clearly fails to meet both of these requirements.

For all of the foregoing reasons, then, the rejection of claims 24 and 25 under 35 U.S.C. §102(e) over Gu is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 1-8, 11-12, 15-17, 20, 23 and 25-27 stand rejected under 35 U.S.C. §102(e) as unpatentable over Johnston in view of Miwa. The Office asserts that applicant's claims are directed to method that entail transfecting cells with a construct "comprising a minimal promoter sequence," and that Johnston discloses that "regulatory sequences which may be used to provide transcriptional control of the gene ... are generally promoters ... and that other regulatory sequences which may optionally be incorporated into the polynucleic acid sequence include enhancers, termination sequences." Office Action at pages 6-7. The Office goes on to note that Johnston exemplifies promotes such as those described by Miwa et al., and then asserts that Miwa "teach a promoter region of the human alpha-cardiac actin gene that lacks an enhancer element, [citing the Miwa abstract]." Office Action at pages 7-8. The Office then concludes that Johnston meets all the limitations of the claims. Applicant respectfully disagrees.

The Office's rejection is based on two grounds, first, that Miwa discloses a minimal promoter, and second, that Johnston teaches optional inclusion of enhancer elements. Both of these grounds are the result of a misinterpretation of the subject references.

With regard to the first ground, that is, the Office's insistence that Miwa "teaches a promoter region of the human alpha-cardiac actin gene that lacks an enhancer element," applicant submits that this conclusion must be based on the last sentence of the abstract that states "this upstream region is not an enhancer but is a tissue-specific regulatory upstream element." See Miwa, abstract. However, if the full abstract is actually read, it becomes clear that Miwa discusses a promoter sequence including sequences -177 to -1 of the human alpha-cardiac actin gene (see

the first sentence of the abstract). Within this promoter sequence, there is an upstream site that was of interest to Miwa et al., that is, the upstream site spanning -140 and -100 and containing specific sequence patterns. These are called CArG motifs (see the second sentence of the abstract). Miwa carried out a series of studies to show that the upstream region -140 to -100 containing the two CArG motifs acts as a tissue-specific regulatory upstream element, and not an enhancer (see the third through last sentence of the abstract). The Office has somehow construed this as a statement that the 177 base promoter of Miwa does not include an enhancer. This is wrong, all that Miwa found was that the -140 to -100 upstream region was not an enhancer. What about the -177 to -141 upstream region? What about the -99 to -1 upstream region? Clearly, this is a misread of the Miwa document.

With regard to the second ground, that is, that is, the Office's insistence that Johnston's reference to optional regulatory elements including enhancers somehow discloses the use of minimal promoters, applicant again submits that this conclusion is absolutely wrong. It is well known in the art that enhancer sequences can be found in 5' locations, 3' locations, and other untranslated regions of the gene, and further that multiple enhancers can act on any single promoter. The Office seeks to turn Johnston's suggestion that further enhancer sequences could be added completely on its head, and somehow arrive at a disclosure of minimal promoters. This is wrong. The skilled artisan would have read Johnston in light of the accepted dogma in the art of nucleic acid immunization that it was essential to have as much expression of the antigen sequence as possible. This is why exceptionally efficient hCMV promoters were favored, they provide a very high level of expression--something that the skilled artsian deemed essential. The skilled artisan would have thus read Johnston's suggestion to mean that further regulatory elements could be used to increase expression, such as additional enhancers. The skilled artisan would not have read Johnston's suggestion of additional regulatory elements to mean that one should use a seemingly disabled promoter, stripped of its native enhancer sequences and thus expected to give much lower expression of antigen and thus

possibly not operate as intended. The Office's interpretation flies in the face of the art-accepted understanding prior to applicant's disclosure.

The Office further argues that "Johnston clearly teach the use of the human alpha-actin promoter disclosed by Miwa ... that lacks an enhancer element [which is a minimal promoter]." Office Action at page 9. However, as discussed above, Miwa does not disclose a minimal promoter, Miwa merely concludes that a portion of the promoter is not an enhancer, but is a tissue-specific regulatory upstream element. Accordingly, Miwa does not disclose a minimal promoter, and Johnston's reference to Miwa thus does nothing to support up the Office's interpretation of Johnston. In fact, applicant notes that the Office refers to the promoter disclosed by Miwa. Applicant respectfully questions which promoter would that be? Miwa discuss a number of deletion mutant promoters. Therefore, it is entirely unclear what Johnston was contemplating when suggesting the use of such an element.

Accordingly, the entire basis for the Office's rejection is the result of misinterpretation of both the primary and the secondary reference relied upon in the rejection. Miwa clearly does not teach a minimal promoter. It is incorrect to read Johnston's suggestion of additional regulatory sequences as some sort of a negative suggestion to use a minimal promoter when the skilled artisan would never have arrived at that interpretation. The Office has relied upon a passage in Johnston that discusses optional regulatory elements (including enhancers), but this passage does not relate to the portions of the specification that are specific to promoters. There is no express disclosure of minimal promoters, and there is no evidence of record in the case that Johnston was inherently referring to native enhancers optionally added to specific promoters. In fact, it is much more plausible that Johnston was referring to the use of additional enhancers such as 3' elements. The mere fact that a certain characteristic *may* have occurred in the prior art is not sufficient to establish the inherency of that characteristic. *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). In fact, for the Office to establish inherency over Johnston, it must identify evidence that makes it clear that the missing descriptive matter (in this case, the

excision of native enhancer sequences from Johnston's promoter) is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). The Office has not established this feature, and the rejection must therefore fail.

For all of the foregoing reasons, then, the rejection of claims 1-8, 11-12, 15-17, 20, 23 and 25 under 35 U.S.C. §102(e) over Johnston is improper and not based upon any proper evidence of record in the instant case. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 1, 12 and 24-27 stand rejected under 35 U.S.C. §102(b) as unpatentable over Burns or Deb. The Office asserts "Burns teach preparation of a ... plasmid comprising a minimal HLA A2 promoter having CCAAT and TATA box motifs operably linked to a CAT gene," and that "Deb disclose a plasmid comprising a minimal human proliferating cell antigen (PCNA) promoter with a TATA box alone operably linked to a CAT gene," and then concludes that Burns and Deb "anticipate the claims." Office Action at page 4. Applicant respectfully disagrees.

As discussed above, anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference. In addition, a prior art reference must be enabling in order to anticipate, thus placing the allegedly disclosed matter in the possession of the public.

All of applicant's claims include the express limitation that a minimal promoter sequence is used to drive expression of the attached antigen sequence. In addition, claim 1 as presently amended recites that the antigen of interest is expressed in a mammalian subject in an amount sufficient that an immune response is elicited against the antigen. Claim 12 depends from claim 1 and thus contain this same base limitation. Claim 24 recites a purified, isolated minimal promoter.

Claim 25 as presently amended recites a vaccine composition containing an antigen sequence operably linked to a minimal promoter. Claims 26 and 27 are cancelled.

Burns and Deb clearly fail to disclose vaccine compositions, and in similar manner fail to disclose administration of nucleic acid compositions to mammals whereby antigen sequences are expressed in an amount sufficient to elicit an immune response. Accordingly, claims 1, 12 and 25 cannot possibly be anticipated by either reference.

With regard to claim 24, Burns clearly fails to disclose a minimal promoter. The Office has disputed this fact, and has asked that applicant point out the exact page and line number that supports this assertion. Office Action at page 5. In response, applicants direct the Office's attention to the sentence bridging pages 1563 and 1564, where the authors state "additional studies using plasmid constructs containing mutated and deleted CCAAT boxes, TATA box, and the consensus sequence are in progress to further define **the *cis*-responsive element in the HLA A2 minimal promoter region**." (Emphasis added.) Accordingly, there is clearly a native enhancer sequence in the Burns "minimal promoter" and this promoter thus fails to meet applicant's expressly defined minimal promoter sequence.

With regard to the Deb reference, the Office seems to argue that the promoter described by Deb is "a minimal PCNA promoter with a TATA box alone operably linked to a CAT gene." Office Action at page 6. The Office thus submits that applicant needs to show factual evidence to show that the PCNA promoters of Deb still contain endogenous or native enhancer sequences. Applicant respectfully that it is the Office's obligation to establish a *prima facie* showing of anticipation before any burden shifts to applicant to rebut the same with a factual showing. What the Office has argued is that the 269 base promoter sequence described by Deb merely contains the TATA box and the promoter. This files in the face of reason since the TATA box is found at about the -30 position, and the promoter is found in the within the -130 position. Accordingly, the Office's position must be that the -269 to -131 region does not contain any native enhancers. Applicant

submits that it is much more plausible that the subject promoter contains enhancer sequences in this upstream region. What the Office certainly has failed to show is that Deb excised all native enhancers from this promoter sequence. There is thus nothing expressly stated by Deb, and there is nothing inherently in the Deb disclosure that teaches or describes applicant's minimal promoters since the mere fact that a certain characteristic *may* have occurred in the prior art is not sufficient to establish the inherency of that characteristic. *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). In fact, for the Office to establish inherency over Deb, it must identify evidence that makes it clear that the missing descriptive matter (in this case, the excision of native enhancer sequences from Deb's promoter) is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). This the Office's legal burden, it has not been met, and this must be met before the burden would transfer to applicant to provide factual evidence to the contrary. The rejection of claim 24 over Deb must therefore fail.

For all of the foregoing reasons, then, the rejection of claims 1, 12, 24 and 25 under 35 U.S.C. §102(b) over Burns or Deb is improper and not based upon any proper evidence of record in the instant case. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

The Rejection under 35 U.S.C. §103(a):

Claims 15 and 21-22 stand rejected under 35 U.S.C. §103(a) as unpatentable over the combination Johnston with evidence of Miwa and in view of Hofmann. In particular, the Office asserts that "Johnston discloses a method for obtaining a protective immune response ... by *in situ* microparticle bombardment by providing microprojectiles carrying a DNA sequence comprising ... a regulatory element functional in the tissue cells and a gene ... coding for an immune response-producing protein or polypeptide" and that "regulatory sequences which may be used to provide transcriptional control of the gene ... are generally promoters ... and

that other regulatory sequences which may optionally be incorporated into the polynucleic acid sequence include enhancers, termination sequences." Office Action at pages 14-15. The Office goes on to note that Johnston exemplifies promotes such as those described by Miwa et al., and then asserts that Miwa "teach a promoter region of the human alpha-cardiac actin gene that lacks an enhancer element, [citing the Miwa abstract]." Office Action at page 15. The Office then acknowledges that "Johnston does not specifically teach ... carrier particles coated with a nucleic acid construct comprising the selected minimal promoter sequence as recited in claims 21 or 22." Office Action at page 15. However, the Office seeks to remedy this by citing Hofmann's tetracycline-inducible promoter system. The Office argues that this would have been obvious to the skilled artisan to modify Johnston with the promoter of Hofmann, and proper motivation would have existed to make this modification since it "would allow one of ordinary skill in the art to regulate the desired levels of transgene in cells *in vivo* under the control of tetracycline for the purpose of obtaining the desired immune responses in a vertebrate." Office Action at page 17. Applicant respectfully disagrees.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicant submits that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over its asserted combination.

As already discussed herein above in regard to the Section 102 rejections, Johnston clearly fails to teach or suggest the use of a minimal promoter. It is simply incorrect to read Johnston's suggestion of additional regulatory sequences as some sort of a negative suggestion to use a minimal promoter when the skilled artisan would never have arrived at that interpretation. There is no express disclosure of minimal promoters, and there is no evidence of record in the case that Johnston was inherently referring to native enhancers optionally added to specific promoters. In fact, it is much more plausible that Johnston was referring to the use of additional enhancers such as 3' elements. This is what the skilled artisan would have understood, that is, that a promoter must be as efficient as possible (e.g., properly enhanced) in order to obtain a very high level of expression. In order to increase expression, the skilled artisan would have added additional enhancers, not stripped them away from their promoters. In order for the Office to support an assertion that Johnston somehow inherently disclosed use of minimal promoters, it must identify evidence that makes it clear that the missing descriptive matter (in this case, the excision of native enhancer sequences from Johnston's promoter) is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

In like manner, Miwa does not disclose a minimal promoter, Miwa merely concludes that a portion of the promoter is not an enhancer, but is a tissue-specific regulatory upstream element. Accordingly, Miwa does not disclose a minimal promoter, and Johnston's reference to Miwa thus does nothing to support up the Office's interpretation of Johnston.

Accordingly, the Office's primary reference combination (Johnston as evidenced by Miwa) is wholly improper and fails to teach or suggest applicant's recited methods. The addition of the secondary reference to Hofmann adds nothing to this primary combination. In fact, the Office's assertion that the skilled artisan would want to use a tetracycline controlled promoter in a nucleic acid vaccine seems

absolutely unsupportable. Why in the world would a skilled person wish to make a vaccine only operate upon the subsequent administration of an antibiotic? There is no plausible scientific or technical argument that supports this assertion.

There is simply no teaching or suggestion in Johnston, Miwa and Hofmann to carry out methods for expressing antigens in mammalian subjects to obtain an immune response, where the antigen sequences are controlled by a minimal promoter. There is no motivation supplied by these references to make the modifications suggested by the Office. There is no reasonable expectation of success that would be held by the skilled artisan. Accordingly, all conceivable combinations of these references still fail to teach or suggest applicant's recited methods that use the instant minimal promoter systems. Accordingly, applicant submits that the Office has failed to establish *prima facie* obviousness over it's proposed combination of Johnston, Miwa and Hofmann.

For these reasons, then, the rejection of claims 15 and 21-22 under 35 U.S.C. §103(a) over Johnston, Miwa and Hofmann is improper. The Office's proposed combination fails to teach or suggest all of applicant's recited limitations. Without the requisite teaching or suggestion, there cannot have been a reasonable expectation for success. Accordingly, *prima facie* obviousness has not been established. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

## CONCLUSION

Applicant respectfully submits that the claims as now pending define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect is earnestly solicited. Applicant further asks that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that the Examiner contact the undersigned in the UK at +44 1865 332 600.

Respectfully submitted,

Date: 18 June 2003

By: _____
Thomas P. McCracken
Registration No. 38,548

POWDERJECT PHARMACEUTICALS PLC
Florey House
The Oxford Science Park
Oxford OX4 4GA
United Kingdom
Telephone: +44 1865 332 600
Fax: +44 1865 332 601

## CURRENT STATUS OF ALL CLAIMS IN THE APPLICATION

What is claimed is:

1. (Amended) A method of obtaining expression of an antigen of interest in a mammalian subject, which method comprises transferring into cells of said subject a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said antigen is expressed in said mammalian cells in an amount sufficient to elicit an immune response to the antigen.

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2. (Previously Amended) The method according to claim 1, wherein the construct is delivered directly into a subject.

3. (Previously Amended) The method according to claim 2, wherein the construct in delivered by injection, transdermal particle delivery, inhalation, topically, intranasally or transmucosally.

4. (Previously Amended) The method according to claim 3, wherein the construct is delivered by needleless injection.

5. (Previously Amended) The method according to claim 1, wherein the construct is delivered *ex vivo* into cells taken from a subject.

6. (Previously Amended) The method according to claim 5, wherein the subject is a human.

7. (Previously Amended) The method according to claim 1, wherein the antigen is a full length protein.

8. (Previously Amended) The method according to claim 7, wherein the antigen is an antigen of a viral, bacterial, parasite or fungal pathogen.

9. (Withdrawn)

10. (Withdrawn)

11. (Previously Amended) The method according to claim 1, wherein the nucleic acid construct is coated onto carrier particles.

12. (Previously Amended) The method according to claim 1, wherein the nucleic acid construct is a DNA construct.

13. (Previously Amended) The method according to claim 1, wherein the minimal promoter sequence consists essentially of a human cytomegalovirus (hCMV) immediate early promoter sequence, a pseudorabies virus (PRV) early promoter region, a simian cytomegalovirus (sCMV) immediate early promoter sequence or a functional variant thereof.

14. (Previously Amended) The method according to claim 13, wherein the minimal promoter sequence consists essentially of the sequence spanning positions 0 to -118 of the hCMV immediate early promoter region or a functional variant of the said spanning sequence.

15. (Original) Coated particles suitable for use in particle-mediated nucleic acid immunisation, which particles comprise carrier particles coated with a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence encoding an antigen.

16. (Original) Coated particles according to claim 15, wherein the carrier particles are tungsten or gold particles.

17. (Original) Coated particles according to claim 15, wherein the antigen is an antigen of a viral, bacterial, parasite or fungal pathogen.

18. (Withdrawn)

19. (Withdrawn)

20. (Original) Coated particles according to claim 15, wherein the nucleic acid construct is DNA construct.

21. (Original) Coated particles according to claim 15, wherein the minimal promoter sequence consists essentially of a human cytomegalovirus (hCMV) immediate early promoter sequence, a pseudorabies virus (PRV) early promoter region, a simian cytomegalovirus (sCMV) immediate early promoter sequence or a functional variant thereof.

22. (Original) Coated particles according to claim 21, wherein the minimal promoter sequence consists essentially of the sequence spanning positions 0 to -118 of the hCMV immediate early promoter region or a functional variant of the said spanning sequence.

23. (Original) A particle acceleration device suitable for particle-mediated nucleic acid immunisation, the said device being loaded with coated particles as defined in claim 15.

24. (Original) A purified, isolated minimal promoter sequence.

25. (Amended) A vaccine composition containing a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen of interest.

26. (Cancelled)

27. (Cancelled)